IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Marchetti et al.
Application No. 10/783,415
Filed: February 19, 2004
Confirmation No. 6397
For: NUCLEOTIDE AND DEDUCED AMINO ACID SEQUENCES OF TUMOR GENE INT6
Examiner: Minh Tam B. Davis
Art Unit: 1614
Attorney Reference No. 4239-67782-01

CERTIFICATE OF MAILING

I hereby certify that this paper and the documents referred to as being attached or enclosed herewith are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450 on the date shown below.

Attorney or Agent for Applicant(s)

Date Mailed December 13, 2005

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

TRANSMITTAL LETTER

Enclosed for filing in the application referenced above are the following:

☒ Declaration of Robert Callahan under 37 C.F.R. § 1.132

☒ The Director is hereby authorized to charge any additional fees that may be required, or credit over-payment, to Deposit Account No. 02-4550. A copy of this sheet is enclosed.

☒ Please return the enclosed postcard to confirm that the items listed above have been received.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By
Susan Alpert Siegel, Ph.D.
Registration No. 43,121

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

SAS:sas 12/13/05 callahan.doc E-265-1994/1-US-04
PATENT

Attorney Reference Number 4239-67782-01
Application Number 10/783,415

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Marchetti et al.
Application No. 10/783,415
Filed: February 19, 2004
Confirmation No. 6397
For: NUCLEOTIDE AND DEDUCED AMINO ACID SEQUENCES OF TUMOR GENE INT6
Examiner:
Art Unit: 1614
Attorney Reference No. 4239-67782-01

CERTIFICATE OF MAILING

I hereby certify that this paper and the documents referred to as being attached or enclosed herewith are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450 on the date shown below.

Attorney or Agent for Applicant(s)

Date Mailed December 13 2005

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

DECLARATION OF ROBERT CALLAHAN UNDER 37 C.F.R. § 1.132

1. I, Robert Callahan, am an inventor of the above-referenced patent application. I have a Ph.D. from Syracuse University, New York, and did a post-doctoral fellowship at the National Institute of Child Health and Human Development in Bethesda, Maryland. I served as the Chief of the Oncogenetics Section of the Laboratory of Tumor Immunology and Biology at the National Cancer Institute of the National Institutes of Health from 1982-2001, and as the Chief of the Oncogenetics Section of the Basic Research Laboratory National Cancer Institute of the National Institutes of Health from 2001-2002. I currently hold the position of Principal Investigator of the Mammary Biology and Tumorigenesis Laboratory National Cancer Institute of the National Institutes of Health. I am an expert in the fields of tumor biology and oncogenetics. A copy of my curriculum vitae is attached.

2. It is my understanding that claims 56-66, which are directed to antibodies that bind Int6, have been rejected as allegedly not having a credible and specific utility. Claims 56-66 are also rejected as allegedly not being enabled by the specification.

3. Tumor-suppressor genes are transcribed into mRNAs which are translated to produce tumor suppressor proteins. In a non-transformed cell, transcription of a tumor suppressor gene and translation of the resultant mRNA into a full-length functional tumor suppressor protein prevents tumors from forming due to the presence of a full-length functional protein. Thus, tumor suppressor proteins function as negative regulators of cell growth and proliferation in non-transformed cells.

Tumor suppressor genes can lose their function due to a DNA mutation. As described in the above-referenced application, mutation in the Int6 gene can result in the loss of the production of Int6 mRNA (see the specification at Example 4, pages 55-56). As the genetic mutations occur at the DNA level, all of the mRNA produced in the cell is affected. If full-length mRNA is not produced, functional suppressor protein cannot be produced. At the time this application was filed, one of skill in the art would know that in the absence of Int6 mRNA, functional Int6 protein could not be present in a tumor cell.

In view of the expectation of one of skill in the art that the absence of full length mRNA is correlated with the absence of functional protein, most investigators chose to only perform an assay for either mRNA or protein in their studies (and not both assays, as this would be considered superfluous). However, the correlation of a decrease in mRNA with a decrease in protein has been demonstrated for another tumor suppressor gene, ras homologue I (ARHI), which is a tumor suppressor gene associated with breast cancer. The loss of ARHI protein is correlated with the loss of ARHI mRNA, as evidenced by Wang et al., (*Clin. Cancer. Res.* 9: 3660-3666, 2003, copy attached). Wang et al. documented that ARHI mRNA and ARHI protein were present in normal breast epithelia. When invasive carcinomas were analyzed, consistent results were obtained when ARHI protein and ARHI mRNA were measured (see the abstract).

For Int6, one of skill in the art would have predicted, at the time the parent application was filed, that in the absence of Int6 mRNA, Int6 protein would not be produced.

4. As a loss of expression of Int6 mRNA was correlated to human breast and lung tumors, it was clearly desirable to purify the Int6 protein and the localization and function of the protein in non-transformed cells. The production of rabbit polyclonal sera to synthetic peptides produced from mouse Int6 is described in the specification on pages 56-57 (note that the amino acid sequence of mouse Int6 is identical to human Int6, which is set forth, for example, in SEQ

ID NO: 4). The use of these isolated antibodies that bind Int6 in Western bloat analyses, protein purification, and immunohistochemistry studies is described in Example 15. The experimental results presented in the specification, and the deposit of two antibodies with the ATCC in accordance with the Budapest Treaty document that antibodies that bind Int6 were fully enabled at the time the application was filed.

5. There have been innumerable publications on Int6 and its role in cell proliferation after the filing of the above-referenced application, as illustrated by Guo et al., *J. Virol.* 74: 1982-1899, 2000; Morris et al., *Oncogene* 24: 1203-1211, 2005; and Watkins et al., *Cell Prolif.* 37: 149-160, 2004. These scientific publications provide documentation that others have demonstrated the usefulness of antibodies that bind Int6 and assays specifically described in the above-referenced patent application.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Robert Callahan, Ph.D.

12/13/2005
Date